Mechanisms of Hydrogen Sulfide against the Progression of Severe Alzheimer’s Disease in Transgenic Mice at Different Ages

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\textbf{Abstract} \\
Background: Alzheimer disease is an age-related severe neurodegenerative pathology. The level of the third endogenous gas, hydrogen sulfide (H\textsubscript{2}S), is decreased in the brain of Alzheimer’s disease (AD) patients compared with the brain of the age-matched normal individuals; also, plasma H\textsubscript{2}S levels are negatively correlated with the severity of AD. Recently, we have demonstrated that systemic H\textsubscript{2}S injections are neuroprotective in an early phase of preclinical AD. Objectives: This study focuses on the possible neuroprotection of a chronic treatment with an H\textsubscript{2}S donor and sulfurous water (rich of H\textsubscript{2}S) in a severe transgenic 3xTg-AD mice model. Method: 3xTg-AD mice at 2 different ages (6 and 12 months) were daily treated intraperitoneally with an H\textsubscript{2}S donor and sulfurous water (rich of H\textsubscript{2}S) for 3 months consecutively. We investigated the cognitive ability, brain morphological alterations, amyloid/tau cascade, excitotoxic, inflammatory and apoptotic responses. Results: Three months of treatments with H\textsubscript{2}S significantly protected against impairment in learning and memory in a severe 3xTg-AD mice model, at both ages studied, and reduced the size of Amyloid β plaques with preservation of the morphological picture. This neuroprotection appeared mainly in the cortex and hippocampus, associated with reduction in activity of c-jun N-terminal kinases, extracellular signal-regulated kinases and p38, which have an established role not only in the phosphorylation of tau protein but also in the inflammatory and excitotoxic response. Conclusion: Our findings indicate that appropriate treatments with various sources of H\textsubscript{2}S might represent an innovative approach to counteract early and severe AD progression in humans.

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